2024 Focused Update: Guidelines on Use of Corticosteroids in Sepsis, Acute Respiratory Distress Syndrome, and Community-Acquired Pneumonia

RATIONALE: New evidence is available examining the use of corticosteroids in sepsis, acute respiratory distress syndrome (ARDS) and community-acquired pneumonia (CAP), warranting a focused update of the 2017 guideline on critical illness-related corticosteroid insufficiency.

OBJECTIVES: To develop evidence-based recommendations for use of corticosteroids in hospitalized adults and children with sepsis, ARDS, and CAP.

PANEL DESIGN: The 22-member panel included diverse representation from medicine, including adult and pediatric intensivists, pulmonologists, endocrinologists, nurses, pharmacists, and clinician-methodologists with expertise in developing evidence-based Clinical Practice Guidelines. We followed Society of Critical Care Medicine conflict of interest policies in all phases of the guideline development, including task force selection and voting.

METHODS: After development of five focused Population, Intervention, Control, and Outcomes (PICO) questions, we conducted systematic reviews to identify the best available evidence addressing each question. We evaluated the certainty of evidence using the Grading of Recommendations Assessment, Development, and Evaluation approach and formulated recommendations using the evidence-to-decision framework.

RESULTS: In response to the five PICOs, the panel issued four recommendations addressing the use of corticosteroids in patients with sepsis, ARDS, and CAP. These included a conditional recommendation to administer corticosteroids for patients with septic shock and critically ill patients with ARDS and a strong recommendation for use in hospitalized patients with severe CAP. The panel also recommended against high dose/short duration administration of corticosteroids for septic shock. In response to the final PICO regarding type of corticosteroid molecule in ARDS, the panel was unable to provide specific recommendations addressing corticosteroid molecule, dose, and duration of therapy, based on currently available evidence.

CONCLUSIONS: The panel provided updated recommendations based on current evidence to inform clinicians, patients, and other stakeholders on the use of corticosteroids for sepsis, ARDS, and CAP.

KEYWORDS: Acute Respiratory Distress Syndrome; Grading of Recommendations Assessment, Development, and Evaluation; community-acquired pneumonia; corticosteroids; critical illness; development; dose-response; glucocorticoids; grading of recommendations assessment; guidelines; mineralocorticoids; sepsis; septic shock

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Dysregulated inflammatory response is common in acutely ill patients requiring hospitalization. Corticosteroids are hypothesized to be beneficial via their broad anti-inflammatory mechanisms. In 2008, a

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multispecialty task force of international experts in critical care medicine and endocrinology from the membership of the Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine introduced the term critical illness-related corticosteroid insufficiency (CIRCI) (1). CIRCI is a state of systemic inflammation with associated dysregulation of the hypothalamus–pituitary–adrenal axis, altered cortisol metabolism, and tissue glucocorticoid resistance (2). This taskforce provided updated guidelines in 2017, issuing recommendations for the diagnosis of CIRCI and management of eight clinical conditions (3, 4). As new studies examining the use of corticosteroids in the acutely ill have been published, there is a need to update recommendations inclusive of recent evidence, especially for the most common of conditions.

Given this need, the SCCM reconvened a panel of international experts to provide updated evidence-based recommendations addressing the use of corticosteroids in the management of acutely ill patients requiring hospitalization. The panel sought to provide recommendations in both adult and pediatric patient populations, as appropriate, based on available evidence. The guideline update focused on sepsis, acute respiratory distress syndrome (ARDS), and community-acquired pneumonia (CAP), which were prioritized as the most common diagnoses in which corticosteroids are considered and those with sufficient new data that reevaluation was warranted. Past guideline recommendations related to the definition and diagnosis of CIRCI were not addressed in this focused update.

METHODOLOGY

Scope and Panel Composition

The SCCM appointed chairs (S.P., D.A.) and co-vice chairs (R.B., A.N.), who along with two clinician methodologists (D.C., B.R.) and methodology team members (T.P., K.D.) from the Guidelines in Intensive Care Development and Evaluation group, collaborated with a panel of 22 experts in corticosteroids and critical illness, to update the previous SCCM/ESICM CIRCI 2017 guidelines (4) (**Supplemental Digital Content 1**, http://links.lww.com/CCM/H475). Two of the 22 panel members were endocrinologists recommended by the Endocrine Society. There were 20 voting members of the panel. Methodology team members (D.C., B.R., T.P., K.D.) participated in data abstraction and analysis and attended panel discussions but did not participate as part of the panel in voting on recommendations. We developed the guideline using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology (5). For this focused update, funding, logistic, and material support was provided solely by SCCM. None of the authors or methodologists received direct financial support to develop this guideline.

Conflict of Interest (COI) Policy

We collected all financial and intellectual COIs from panel members according to the American College of Critical Care Medicine/SCCM Standard Operating Procedures, which were reviewed and managed by SCCM (**Supplemental Digital Content 2**, http://links.lww.com/CCM/H475). A guideline chair and panel participant (D.A.) disclosed academic conflicts of interest. He participated in the discussion for corticosteroids in sepsis but abstained from voting on final recommendations pertaining to corticosteroids in sepsis and septic shock.

Question Development and Outcome Prioritization

Following initial discussions, we identified five actionable Patients, Intervention, Comparator, Outcomes (PICO) questions related to the use of corticosteroids in critical illness (**Table 1**, **Supplemental Digital Content 3**, http://links.lww.com/CCM/H475). These PICO questions were largely derived and slightly modified from the PICO questions of the 2017 guidelines. The panel also generated a list of outcomes that were prioritized based on perceived patient importance (**Supplemental Digital Content 4**, http://links.lww.com/CCM/H475) (6). Unfortunately, due to limited data reported in the included studies, we were unable to include all outcomes generated by the panel (for a list of prioritized outcomes, see evidence summaries in **Supplemental Digital Content 9**, http://links.lww.com/CCM/H475).

Systematic Review and Meta-Analysis

Working with a medical librarian, we conducted systematic reviews of the literature to identify studies relevant to each of the five PICO questions (**Supplemental Digital Content 5**, http://links.lww.com/CCM/H475).

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TABLE 1.
Population, Intervention, Control, and Outcomes Questions

Population	Intervention	Comparison	Outcomes
Should corticosteroids be administered to hospitalized patients with sepsis?			
All adult and pediatric patients with sepsis	Corticosteroids	Placebo or no corticosteroids	Supplemental Digital Content 4 (http://links.lww.com/CCM/H475)
If patients with sepsis are administered corticosteroids, should high dose/short duration or low dose/long duration be used?			
All adult and pediatric patients with sepsis	High dose/short duration	Low dose/long duration	Supplemental Digital Content 4 (http://links.lww.com/CCM/H475)
Should corticosteroids compared with no corticosteroids be used in patients with ARDS?			
All adult and pediatric patients with ARDS	Corticosteroids	Placebo or no corticosteroids	Supplemental Digital Content 4 (http://links.lww.com/CCM/H475)
Should methylprednisolone be used over other corticosteroids in patients with ARDS?			
All adult and pediatric patients with ARDS	Methylprednisolone	Dexamethasone, hydrocortisone	Supplemental Digital Content 4 (http://links.lww.com/CCM/H475)
Should corticosteroids be administered to hospitalized patients with CAP?			
All adult and pediatric patients with CAP	Corticosteroids	Placebo or no corticosteroids	Supplemental Digital Content 4 (http://links.lww.com/CCM/H475)

ARDS = Acute Respiratory Distress Syndrome, CAP = community-acquired pneumonia.

Four of the five PICO questions (those related to ARDS and sepsis) had recent systematic reviews conducted by co-authors of this guideline and thus only required updated searches (7, 8). Using Covidence, a systematic review management software, a team of reviewers (D.C., T.P., K.D.) screened titles and abstracts and subsequently full-text manuscripts independently and in duplicate. We performed data extraction and risk of bias assessment independently and in duplicate for each included trial as per standard systematic review methodology (**Supplemental Digital Content 6**, http://links.lww.com/CCM/H475). We used Revman, v.5.3, software for pooled analysis, inverse variance weighting and random effects models. We performed assessment of the certainty in the evidence for each question and outcome using GRADE methodology (5) and generated evidence profiles using GRADEPro Guideline Development Tool (www.gradepro.org, **Supplemental Digital Content 7**, http://links.lww.com/CCM/H475). We used the Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN) tool to establish the credibility of any subgroup effects (9).

Formulation of Recommendations

We developed recommendations using the GRADE Evidence-to-Decision (10) framework, which considers the certainty in the evidence, the balance between desirable and undesirable effects (positive effects and negative effects), patient values and preferences, resource use, health equity, acceptability, and feasibility. We designated recommendations as strong (using the phrasing "we recommend") or conditional (using the phrasing "we suggest"). **Table 2** describes the implications of the strength of a recommendation. After data analysis and panel discussion, the panel elected to not provide a specific recommendation related to the PICO question that addressed corticosteroid molecules in ARDS. Elaboration on panel discussions is provided in the rationale below.

Voting Process

Panel members reviewed and approved all recommendations and rationales by a formal web-based vote. Panel members unable to join the teleconferences due to time zone differences were expected to review the recordings of the teleconferences and provided opportunity for input electronically. We defined consensus as 80% agreement among at least 75% of panel members (**Supplemental Digital Content 8**, http://links.lww.com/CCM/H475).

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TABLE 2.
Grading of Recommendations Assessment, Development, and Evaluation Classification of Strengths of Recommendations and Their Implications

Implications for…	Strong Recommendation "We recommend…"	Conditional Recommendation "We suggest…"
	Desirable effects of intervention clearly outweigh undesirable effects, or clearly do not.	**Trade-offs are less certain, either because of low-quality evidence or because evidence suggests desirable and undesirable effects are closely balanced.**
… patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not
… clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices are likely to be appropriate for different patients, and therapy should be tailored to the individual patient's circumstances. Those circumstances may include the patient or family's values and preferences
… policymakers	The recommendation can be adapted as policy in most situations, including for use as performance indicators.	Policymaking will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place

RECOMMENDATIONS

The panel generated four recommendations which are summarized in **Table 3**. Panel recommendations pertain to adult patients. We were unable to make specific recommendations in the pediatric population due to limited available studies.

Corticosteroids in Sepsis and Septic Shock

Recommendation.

1A) We "suggest" administering corticosteroids to adult patients with septic shock (conditional recommendation, low certainty).

1B) We "recommend against" administration of high dose/short duration corticosteroids (> 400 mg/d hydrocortisone equivalent for < 3 d) for adult patients with septic shock (strong recommendation, moderate certainty).

Remark. We make no recommendation for corticosteroid use in pediatric patients with sepsis.

Rationale.

Evidence Summary. A total of 46 randomized control trials (RCTs) (11–56) compared corticosteroids to placebo or standard care in patients with sepsis or septic shock. Overall, seven trials included patients with sepsis (21, 24, 33, 48, 50, 51, 53), five included patients with CAP and sepsis (14, 28, 35, 38, 46), another four included patients with ARDS and sepsis (22, 26, 32, 44) and the remainder included patients with septic shock. Six trials examined pediatric patients (16, 17, 29, 37, 47, 54), one included both adults and children (15), whereas the remainder included only adults. Trials varied in type of corticosteroid used, dosage and duration of therapy. See Supplemental Digital Content 9***A*** (http://links.lww.com/CCM/H475) for the GRADE evidence profile and characteristics of included trials.

Corticosteroid use may reduce hospital/long-term mortality (from 60 d to 1 yr) (relative risk [RR] 0.94; 95% CI, 0.89–1.00, low certainty) and probably reduces ICU/short-term mortality (14–30 d) (RR 0.93; 95% CI, 0.88–0.98, moderate certainty) in patients with sepsis or septic shock. Subgroup analysis based on corticosteroid type, duration of therapy, or corticosteroid dosage did not demonstrate any credible subgroup effects. Subgroup analysis comparing sepsis and septic shock

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TABLE 3.
Summary of Recommendations[a]

Recommendation 2024	Recommendation Strength, Quality of Evidence	Comparison to 2017 Recommendations
Sepsis and septic shock		
1A. We "suggest" administering corticosteroids to adult patients with septic shock	Conditional recommendation, low certainty evidence	We suggest against corticosteroid administration in adult patients with sepsis without shock (conditional recommendation, moderate quality of evidence)
1B. We "recommend against" administration of high dose/short duration corticosteroids (> 400 mg/d hydrocortisone equivalent for less than 3 d) for adult patients with septic shock (strong recommendation, low certainty)	Strong recommendation, moderate certainty evidence	We suggest using corticosteroids in patients with septic shock that is not responsive to fluid and moderate- to high-dose vasopressor therapy (conditional recommendation, low quality of evidence)
Acute respiratory distress syndrome		
2A. We "suggest" administering corticosteroids to adult hospitalized patients with acute respiratory distress syndrome	Conditional recommendation, moderate certainty evidence	We suggest use of corticosteroids in patients with early moderate to severe acute respiratory distress syndrome (PaO_2/FIO_2 of < 200 and within 14 d of onset) (conditional recommendation, moderate quality of evidence)
Community-acquired bacterial pneumonia		
3A. We "recommend" administering corticosteroids to adult patients hospitalized with severe bacterial community-acquired pneumonia	Strong recommendation, moderate certainty evidence	We suggest use of corticosteroids for 5–7 d at a daily dose < 400 mg IV hydrocortisone or equivalent in hospitalized patients with community-acquired pneumonia (conditional recommendation, moderate quality of evidence)
3B. We make "no recommendation" for administering corticosteroids for adult patients hospitalized with less severe bacterial community-acquired pneumonia	No recommendation	

[a]Remark: We make no recommendation for corticosteroid use in pediatric patients with sepsis and septic shock, acute respiratory distress syndrome, and community-acquired pneumonia.

showed no interaction for short-term mortality (p value for subgroup interaction = 0.08). Corticosteroids may reduce ICU (mean difference [MD] 0.60 d fewer; 95% CI, 1.48 d fewer to 0.27 d more, low certainty) and hospital (MD 0.74 d fewer; 95% CI, 2.06 d fewer to 0.57 d more, low certainty) length of stay. Corticosteroid use may increase neuromuscular weakness (RR 1.21; 95% CI, 1.01–1.45, low certainty), probably increase hypernatremia (RR 1.64; 95% CI, 1.32–2.03, moderate certainty) and hyperglycemia (RR 1.13; 95% CI, 1.08–1.18, moderate certainty) and may reduce neuropsychiatric effects (RR 0.58; 95% CI, 0.33–1.03, low certainty). There is an uncertain effect on gastrointestinal (GI) bleeding (very low certainty), superinfection (very low certainty), stroke (very low certainty), and myocardial infarction (very low certainty). The use of corticosteroids results in higher rates of shock reversal (RR 1.24; 95% CI, 1.11–1.38, high certainty) and reduced organ dysfunction (MD 1.41 points lower Sequential Organ Failure Assessment score; 95% CI, 0.96 points lower to 1.87 points lower, high certainty) at 7 days.

Evidence to Recommendation. The panel felt that corticosteroids offered small to moderate desirable effects, particularly in patients with septic shock. Although the effect sizes for short- and long-term mortality were not as large as those for CAP or ARDS, the reduction in organ dysfunction and shock reversal have important implications from a hospital resource perspective. Further given the high prevalence and

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mortality of septic shock worldwide (57, 58), even a smaller relative effect can translate to large absolute effects. Undesirable effects are anticipated to be small. Adverse effects such as neuromuscular weakness, hypernatremia, and hyperglycemia were defined variably across studies and thus their true impacts on patients are unclear, especially long term. However, given the importance of neuromuscular weakness as a patient-centered outcome, even a small increase in this outcome may be important. The panel also noted that corticosteroids seemed to be protective for neuropsychiatric effects. Although there is some signal toward using corticosteroids for psychiatric conditions (59–61), further study is needed. Overall, the panel felt the balance of effects probably favored corticosteroid use in patients with septic shock, driven by the small to moderate desirable effects and the uncertainty in undesirable effects.

One study (62) found that hydrocortisone in septic shock had no effect on long-term costs or cost-effectiveness based on data from the ADRENAL trial (49). However, this study only used data from one of the 46 RCTs that enrolled patients with septic shock in New Zealand. Corticosteroids are known to be inexpensive, and if their use translates into a reduced need for organ support, and reduced lengths of stay, these would be important factors in reducing healthcare costs with sepsis. The panel felt that use of corticosteroids was feasible and acceptable to healthcare providers.

Special Considerations. The 2017 SCCM/ESICM guideline recommended use of corticosteroids in patients with septic shock that is not responsive to fluid and moderate- to high-dose vasopressor therapy (4). This panel decided that the evidence shows benefit of corticosteroids in patients with septic shock requiring vasopressors, regardless of dose (12, 49, 63). Subgroup analysis considering contemporaneous studies as compared with more historical studies which used over 400 mg/day of hydrocortisone equivalent for less than 3 days do not support the use of this high dose/short duration regime given the risk of adverse effects, thereby substantiating the panel's recommendation against these regimens. Recommendations for corticosteroid use in sepsis have uncertain generalizability to children as there were limited studies available evaluating this population. Although the panel did not make a specific recommendation regarding corticosteroid use in sepsis without shock, if patients present with sepsis and severe CAP or sepsis with ARDS, we suggest administering corticosteroids as per respective recommendations. Based on available data, the panel did not recommend a specific corticosteroid or dosing regimen. The most common doses used in studies evaluating patients with septic shock are IV hydrocortisone 200–300 mg/d, in divided doses or as a continuous infusion, for 5–7 days, with or without a taper (**Table 4**; and Supplemental Digital Content 9*A*, http://links.lww.com/CCM/H475). Some studies included fludrocortisone 50 μg enterally daily, in addition to hydrocortisone. A patient-level meta-analysis of RCTs (63) using low-dose hydrocortisone in adult patients with septic shock suggests a mortality benefit in regimens that combined fludrocortisone with hydrocortisone versus hydrocortisone alone. The credibility of the subgroup finding is unclear, and our analysis did not show a difference based on mineralocorticoid potency, thus no specific recommendations on use of fludrocortisone were made.

Corticosteroids in Acute Respiratory Distress Syndrome

Recommendations.

2A) We "suggest" administering corticosteroids to adult critically ill patients with ARDS (conditional recommendation, moderate certainty).

Remark. We make no recommendation for corticosteroid use in pediatric patients with ARDS.

Rationale.

Evidence Summary. Eighteen RCTs (22, 26, 32, 44, 64, 65, 69–76) compared corticosteroids to placebo or standard care in adult hospitalized patients with ARDS. Twelve (67%) of the RCTs included patients with American-European Consensus Conference or Berlin Conference criteria for ARDS (22, 26, 32, 44, 64, 65, 69, 72–76), and 6 (33%) included patients with COVID-19 (70, 71, 75). Trials varied in type of corticosteroid used, corticosteroid initiation time, dosage, and duration of therapy. See **Supplemental Digital Content 9*B*** (http://links.lww.com/CCM/H475) for the GRADE evidence profile and characteristics of included trials.

Corticosteroid use probably reduces 28-day mortality (RR 0.82; 95% CI, 0.72–0.95, moderate certainty) in critically ill patients with ARDS. Subgroup analysis based on COVID-19 status, corticosteroid type, dosage, and initiation time did not demonstrate any credible

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TABLE 4.
Corticosteroid Dosing Regimens

Disease State	Common Corticosteroid Regimens
Septic shock	Hydrocortisone 200 mg IV per day (continuous infusion or divided every 6 hr) with or without fludrocortisone 50 µg enteral daily for 7 d or until ICU discharge[a]
ARDS	Early ARDS (within 24 hr) Dexamethasone 20 mg IV daily for 5 d, then 10 mg IV daily for 5 d until extubation (64) Early ARDS (within 72 hr) (65) Methylprednisolone 1 mg/kg IV bolus, then • Days 1–14: 1 mg/kg/d continuous infusion • Days 15–21: 0.5 mg/kg/d • Days 22–25: 0.25 mg/kg/d • Days 26–28: 0.125 mg/kg/d • If extubated between days 1 and 15 then advance to day 15 of regimen Unresolving ARDS (7–21 d) (26) Methylprednisolone 2 mg/kg IV bolus, then • Days 1–14: 2 mg/kg/d divided every 6 hr • Days 15–21: 1 mg/kg/d • Days 22–28: 0.5 mg/kg/d • Days 29–30: 0.25 mg/kg/d • Days 31–32: 0.125 mg/kg/d • If extubated before day 14, then advance to day 15 of regimen drug therapy
Severe community-acquired bacterial pneumonia	Hydrocortisone 200 mg IV once, then 10 mg/hr IV infusion for 7 d (14, 66) Hydrocortisone 200 mg IV daily (for 4 or 8 d based on clinical improvement), then taper (for a total duration of 8 or 14 d duration) (67) • Hydrocortisone discontinued on ICU discharge Methylprednisolone 0.5 mg/kg IV every 12 hr for 7 d (within 36 hr of hospital admission, C-reactive protein >150 mg/L) (46) Methylprednisolone 40 mg IV bolus, then • Days 1–7: 40 mg/d • Days 8–14: 20 mg/d • Days 15–17: 12 mg/d • Days 18–20: 4 mg/d • Administered via continuous infusion in ICU, then changed two divided bid, via IV or enteral, after ICU discharge (68)

[a]Duration varies; regimens used in largest and most recent randomized studies (12, 49).
Complete list of corticosteroid regimens included in studies available in Supplemental Digital Content 9 (http://links.lww.com/CCM/H475).

subgroup effects. Patients who received a longer course of corticosteroids (> 7 d) had higher rates of survival than those who received a shorter course (7 d or less) (p value for subgroup interaction = 0.04, moderate credibility). The use of corticosteroids may lead to fewer days of mechanical ventilation (low certainty) and a shorter hospital length of stay (low certainty). There was an uncertain effect on ICU length of stay (very low certainty), neuromuscular weakness (very low certainty) and GI bleeding (low certainty) with corticosteroids. There was probably an increase in hyperglycemia (RR 1.11; 95% CI, 1.01–1.23, moderate certainty).

Evidence to Recommendation. The panel decided that corticosteroids offered moderate desirable effects, driven primarily by moderate certainty evidence that corticosteroids reduce mortality and low certainty evidence that they reduce hospital length of stay and duration of mechanical ventilation. Ongoing uncertainty was driven by the fact that a few small positive trials had a large contribution to the overall positive effect of corticosteroids, lack of long-term outcome data, and that half of the included patients had COVID-19 ARDS. The undesirable effects of short-term corticosteroids remain largely unknown and need further

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study. Although corticosteroids probably increase hyperglycemia, it was variably defined across studies, can be managed short-term with pharmacologic intervention, and the longer-term effects of hyperglycemia are uncertain. Furthermore, the effects on GI bleeding, neuromuscular weakness, secondary infections, and neuropsychiatric effects remain unclear. Overall, the panel felt that the balance of favorable and unfavorable effects probably favored the use of corticosteroids in ARDS.

There were no studies examining the cost-effectiveness of corticosteroids in ARDS. The panel felt that there may be short-term cost savings given the decrease in duration of mechanical ventilation but potential long-term costs, given the potential increase in neuromuscular weakness and other undesirable effects of corticosteroids. The panel felt that corticosteroid use would be feasible and acceptable to healthcare providers.

Special Considerations. As with sepsis, recommendations for corticosteroid use in ARDS have uncertain generalizability to children as there were no RCTs available in this population. The 2017 SCCM/ESICM guidelines had previously recommended giving methylprednisolone 1 mg/kg/d within 14 days of the diagnosis of moderate to severe ARDS (Pao_2/Fio_2 ratio of < 200) (4). This panel, based on pooled estimates which also included patients with ARDS from COVID-19, decided to remove the qualifier based on Pao_2/Fio_2 ratio from the most recent recommendation. Further, updated analysis did not demonstrate a differential effect based on corticosteroid timing or type or dosage [including in direct head-to-head comparisons (77, 78). Given there were no subgroup effects, a specific recommendation was not made for corticosteroid molecules (methylprednisolone or other). Method of administration (intermittent vs continuous) was included in our corticosteroid dosing regimen (Table 4) but not specifically addressed further due to small sample size of patients who received continuous interventions. The panel recognized that multiple dosing strategies are acceptable and specific choices are better left to clinician discretion and other considerations, pending further data. Dosing regimens range from 40 mg/d to 2 mg/kg/d IV methylprednisolone equivalent with a common duration ranging from 7 to 30 days. Methylprednisolone, dexamethasone, and hydrocortisone with or without fludrocortisone are the most common corticosteroid molecules included in RCTs. Common dosing regimens used in RCTs are included in Table 4, with a complete list of corticosteroid regimens listed in Supplemental Digital Content 9*B* (http://links.lww.com/CCM/H475).

Corticosteroids in Community-Acquired Pneumonia

Recommendations.

3A) We "recommend" administering corticosteroids to adult patients hospitalized with severe bacterial CAP (strong recommendation, moderate certainty).

3B) We "make no recommendation" for administering corticosteroids for adult patients hospitalized with less severe bacterial CAP.

Remark. We make no recommendation for corticosteroid use in pediatric patients with CAP.

Rationale.

Evidence Summary. Eighteen RCTs compared corticosteroids to no corticosteroids in adult hospitalized patients with suspected or probable bacterial CAP, including severe and less severe disease (79). Severe CAP was classified as severe if 50% or more of participants had severe pneumonia (Pneumonia Severity Index of IV or V, Confusion, urea nitrogen, respiratory rate-65 scores of ≥ 3, confusion, oxygenation, respiratory and blood pressure scores of ≥ 22, or systolic blood pressure, multilobar chest radiography, albumin, respiratory rate, tachycardia, confusion, oxygenation, arterial pH scores of ≥ 4) or if most patients were admitted to the ICU at the time of randomization or required IV continuous vasopressor therapy (**Supplemental Digital Content 9*C***, http://links.lww.com/CCM/H475). Overall, 10 trials were classified as severe disease (14, 35, 46, 66–68, 80–83) and 8 trials as less-severe disease (38, 84–90) and within-study subgroup data were available from two trials addressing severity (38, 88).

In patients with severe CAP, corticosteroids probably reduce hospital mortality (RR 0.62; 95% CI, 0.45–0.85; moderate certainty), an effect not seen in less severe CAP (RR 1.08; 95% CI, 0.83–1.42; low certainty) (subgroup interaction based on severity $p = 0.01$, moderate credibility as assessed using the ICEMAN tool). There was also a subgroup effect on mortality based on corticosteroid molecule (subgroup interaction based on corticosteroid $p < 0.001$, moderate/low credibility as assessed using the ICEMAN tool).

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In all hospitalized patients with CAP (severe and less severe), corticosteroids probably reduce need for invasive mechanical ventilation (moderate certainty) and may decrease duration of ICU (low certainty) and hospital stay (low certainty). For outcomes other than mortality, there was no subgroup effect based on severity or corticosteroid molecule.

In all patients hospitalized with CAP, corticosteroids probably increase the risk of hyperglycemia (moderate certainty), may increase secondary infections (low certainty), but have uncertain effects on GI bleeding (low certainty). See Supplemental Digital Content 9*C* (http://links.lww.com/CCM/H475) for evidence profile.

Evidence to Recommendation. There was general agreement among the panel for a credible subgroup effect demonstrating a large desirable treatment effect of corticosteroid use for patients with severe CAP with less magnitude of benefit in less severe CAP. Given this subgroup effect, the panel decided to make separate recommendations for severe and nonsevere CAP. Undesirable effects are anticipated to be small across severity of illness. Although hyperglycemia was increased with corticosteroids, due to variable definitions across studies, the impact of this as a patient-centered outcome is unclear. Despite an increase in secondary infections, the panel was reassured by no negative impact on clinical outcomes such as ventilator-free days or length of stay. As with the previous recommendations, the panel acknowledged a degree of uncertainty that still exists due to the lack of systematic evaluation of adverse effects and the risk of amplification of adverse effects not seen in RCTs. Overall, the panel felt that the balance of beneficial and undesirable effects favors giving corticosteroids to patients with more severe CAP but was uncertain in patients with less severe CAP. This judgment was also driven in part by the recent publication of the Community-Acquired Pneumonia: Evaluation of Corticosteroids (CAPE COD) trial, the largest RCT on the topic, which represented approximately 35% of the severe CAP subgroup patients and showed a strong mortality benefit with the use of corticosteroids (67). Corticosteroids are inexpensive and widely available, which could possibly improve equity compared with more expensive interventions. Of note, 2 of the 18 RCTs included in our analysis were done in low- to middle-income countries (35, 66).

Evidence informing cost-effectiveness of systemic corticosteroids in CAP is lacking. One study suggests cost savings associated with administration of corticosteroids and a more pronounced benefit in those with severe CAP (91). Overall use of corticosteroids was felt to be acceptable and feasible.

Definitions for severe CAP and use of risk stratification scores are variable across RCTs and remain an area of study (study severity assignment for meta-analysis included in Supplemental Digital Content 9*C*, http://links.lww.com/CCM/H475). **Table 5** includes examples of available risk stratification scores, or criteria used in RCTs. Although the panel considered a conditional recommendation against corticosteroids in less severe diseases, we ultimately did not achieve consensus on this, given some endpoints suggested benefits, albeit of lower magnitude and in more subjective outcomes. Further RCTs evaluating the role of corticosteroids in patients with less severe CAP are urgently needed.

Special Considerations. As with sepsis and ARDS, the panel was unable to make any statements on the use of corticosteroids in CAP in children based on the lack of RCTs on this topic. The recommendation for bacterial CAP does not require microbiologic confirmation, but rather refers to patients that have high clinical suspicion for bacterial pneumonia treated with empiric antibiotics. Further, globally CAP has variable microbiology, thus it is uncertain if corticosteroid effects are generalizable to other etiologies of CAP.

The 2017 SCCM/ESICM guideline recommended corticosteroids for 5–7 days at a daily dose < 400 mg IV hydrocortisone or equivalent. The current evidence did not demonstrate a differential effect based on corticosteroid duration and showed a possible subgroup interaction on mortality based on corticosteroid molecule; however, this analysis included both severe and nonsevere CAP. The updated recommendation recognizes that multiple dosing strategies are acceptable for severe CAP and likely related to clinician discretion, pending further data. Typical doses range from 40 to 80 mg/d IV methylprednisolone equivalent for a duration of 5–7 days, with one study including a prolonged taper over 20 days, and one guided by clinical criteria for 8 or 14 days (actual median [interquartile range] duration 5 (68) d). Example dosing regimens for severe CAP used in RCTs are provided in Table 3 and a complete list of regimens is included in Supplemental Digital Content 9*C* (http://links.lww.com/CCM/H475).

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TABLE 5.
Severe Community-Acquired Pneumonia Definitions

Source	Definition
American Thoracic Society/ Infectious Diseases Society of America Criteria 2007[a] (92)	Either one major criterion or three or more minor criteria: Major criteria • Septic shock with need for vasopressors • Respiratory failure requiring mechanical ventilation Minor criteria • Respiratory rate ≥ 30 breaths/min[b] • Pao_2/Fio_2 ratio ≤ 250[b] • Multilobar infiltrates • Confusion/disorientation • Uremia (blood urea nitrogen level ≥ 20 mg/dL) • Leukopenia (WBC count < 4000 cells/μL)[c] • Thrombocytopenia (platelet count < 100,000/μL) • Hypothermia (core temperature < 36°C) • Hypotension requiring aggressive fluid resuscitation
Community-Acquired Pneumonia: Evaluation of Corticosteroids (CAPE COD) (67)	One of four criterion: • Initiation of mechanical ventilation (invasive or noninvasive) with a positive end-expiratory pressure level of at least 5 cm of water • Administration of oxygen through a high-flow nasal cannula with a Pao_2/Fio_2 ratio of < 300, with a Fio_2 of ≥ 50% • Nonbreathing mask with estimated Pao_2/Fio_2 of < 300, according to prespecified charts • Pulmonary Severity Index score of > 130 (group V) Inclusion in study required ICU admission
Risk Stratification Scores	• Pneumonia severity index class IV or V (93) • Confusion, urea nitrogen, respiratory rate, blood pressure-65 score of ≥ 3 (94) • Confusion, oxygenation, respiratory and blood pressure score of ≥ 2 (95) • Systolic blood pressure, multilobar chest radiography, albumin, respiratory rate, tachycardia, confusion, oxygenation, arterial pH score ≥ 3 (96)

[a]Studies used previous iterations of ATS criteria modified by Ewig et al (97).
[b]A need for noninvasive ventilation can substitute for a respiratory rate ≥ 30 beats/min or a Pao_2/Fio_2 ratio ≤ 250.
[c]As result of infection alone.

RESEARCH AGENDA

- The administration of corticosteroids for septic shock, ARDS, and CAP in children.
- The use of corticosteroids in patients with surgical sepsis without shock, as this subgroup was underrepresented in included RCTs and theoretical harms exist in this population with regards to wound healing and anastomosis.
- The administration of corticosteroids in patients with neurologic issues and sepsis, has given conflicting evidence for harm or benefit in this population.
- The role of corticosteroids in hospitalized patients with less severe CAP.
- The use of precision medicine and enrichment, including patient phenotypes and genotypes most likely to benefit from corticosteroid administration for sepsis and septic shock, ARDS, and CAP.
- The evaluation of patient-specific factors that impact duration of corticosteroid use for sepsis and septic shock, ARDS, and CAP.
- Cost-effectiveness of corticosteroids in various healthcare systems.
- Patient/family views and involvement regarding the use of corticosteroids in critical illness, particularly in determining patient-important outcomes.
- The optimal dose and duration need to be evaluated in sepsis, CAP and ARDS, generally and in different subpopulations of critically ill patients.
- Long- and short-term consequences of corticosteroid use, such as neuromuscular weakness, neuropsychiatric effects, and secondary infections.
- The use of corticosteroids for prevention of neuropsychiatric morbidity in critically ill patients with sepsis, CAP, and ARDS.
- Develop understanding of the underlying mechanism of action of corticosteroids in critical illness.

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